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Evaluation of mineralization balance in patients with hypoparathyroidism

Duygu Felek[1] Onur İlkay Dinçer[2]

[1]Department of Internal Medicine, Sorgun State Hospital, Yozgat, Turkey
[2]Department of General Surgery, Sorgun State Hospital, Yozgat, Turkey

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Corresponding Author: Duygu Felek, d.kocamemik@gmail.com

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ABSTRACT

Aims: Surgical complications play a major role in the etiology of hypoparathyroidism. Calcium and phosphorus metabolisms are disrupted by hypoparathyroidism. As a result, bone mineralization is impaired and may cause many pathologies. In clinical practice, parathyroid transplantation is not possible in every patient. In this study, we aimed to evaluate whether it would be possible to prevent the complications caused by hypoparathyroidism with mineral-supplemented medical therapy, even if we could not replace the lost parathyroid tissue.

Methods: A total of 79 individuals with hypoparathyroidism (parathormone levels below the reference range for more than one year) secondary to thyroidectomy admitted to our hospital were included in the study. Calcium, phosphorus, alkaline phosphatase (ALP), vitamin D, and creatinine levels were recorded in the last three controls. The relationship between parathormone levels, mineral levels, and ALP, which is an indicator of bone turnover, was analyzed.

Results: The mean calcium value was 8.57±0.90 and the mean phosphorus value was 4.46±0.99 in individuals diagnosed as hypoparathyroid with biochemical data. When the relationship between parathormone and the average of the last three calcium values, the relationship between the average phosphorus value, and the relationship between ALP and vitamin D were examined, no significant difference was found ($p<0.05$). When the relationship between the calcium phosphorus product and its effect on bone mineralization was examined, the mean calcium phosphorus product was 37.64±7.37, and no statistically significant difference was found with parathormone level ($p<0.05$).

Conclusion: Preservation of parathyroid tissue is important for calcium-phosphorus metabolism. Although loss of parathyroid tissue is irreversible, it may be possible to prevent complications with mineral supplementation. As long as calcium and phosphorus balance are maintained externally, bone turnover will be preserved, along with many pathologies caused by hypocalcemia. No matter how low the parathormone level is, the bone mineralization problem caused by hypoparathyroidism can be reduced or even eliminated with mineral levels normalized with medical treatment.

Keywords: Hypoparathyroidism, bone mineralization, hypocalcemia

INTRODUCTION

Hypoparathyroidism is an endocrinologic disorder characterized by congenital or acquired deficiency or absence of parathormone (PTH) secretion, resulting in multisystemic pathologies affecting calcium-phosphorus metabolism. Its prevalence has been found to be 0.37% in the USA and 0.22% in Europe. In Turkey, its prevalence is unknown.[1] The diagnosis is made by biochemical methods and the measurement of serum PTH levels. In the absence of PTH, ionized calcium levels decrease; PTH levels should be controlled in cases of hypocalcemia.[2]

The most common cause of hypoparathyroidism is iatrogenic, secondary to neck surgery. In particular, hypoparathyroidism develops in approximately 10% of patients as a result of complications secondary to thyroidectomy. While 8.3% of these are transient, permanent PTH deficiency occurs in 1.7%. However, these rates have been found to be lower in clinics with more frequent thyroid surgery.[3]

As a result of hypoparathyroidism, serious complications may develop as a result of electrolyte disorders such as calcium deficiency and high phosphate levels. All patients with calcium level below 8 mg/dl should be treated. The aim of treatment is to increase calcium levels through calcium and vitamin D supplements.[4] Although not yet proven, gene therapy has recently attracted attention among treatment options. Parathyroid transplantation is another treatment option.[5] Another proven treatment is the use of PTH analogs; however, this treatment can be used if there is no response to vitamin D and calcium. The goal of treatment should be to maintain calcium levels just below the reference value; however, the dose may be increased if the patient describes symptoms. Phosphorus and magnesium levels should also be

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kept within reference limits. The calcium-phosphorus product should be below 55 to prevent metastatic calcifications.[6]

Since hypoparathyroidism causes low bone turnover, it may lead to osteoporosis; bone mineralization is impaired, and the risk of bone fracture increases. In our study, we aimed to determine the conditions affecting bone mineralization in individuals with hypoparathyroidism and to draw attention to what should be done to minimize these conditions.

METHODS

Ethics

The study was initiated after the decision of the Yozgat Bozok University Clinical Ethics Committee 2017-KAEK-189_2022.11.10_07. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Institutional approval was obtained before the study.

Design

The study was planned as a retrospective cross-sectional study.

Patients

All data were collected after ethics committee approval.

Inclusion Criteria

Adult individuals admitted to our hospital between 2017 and 2022 and diagnosed with hypoparathyroidism secondary to thyroidectomy were included in the study.

Exclusion Criteria

Individuals with known renal failure, a diagnosis of obesity, endocrine pathology that may cause osteoporosis, and drug use that may affect bone turnover were excluded.

Methods

Age, gender, creatinine, PTH, calcium, phosphorus, and ALP values were recorded. Calcium values were averaged by recording the last three calcium measurements in order to reflect accurate results. The calcium-phosphorus product was calculated.

Statistical Analysis

The SPSS program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements were summarized as mean and standard deviation. The normal distribution of the measurements was evaluated by the Shapiro Wilk and Kolmogorov Smirnov tests. Statistical differences between independent variables were evaluated with the Student-t test and one-way ANOVA tests for parametric data and Mann-Whitney U and Kruskal-Wallis tests for nonparametric data. A paired t test was used for statistical evaluation of parametric data between dependent variables. Pearson and Spearman correlation analyses were used for correlation evaluations between two measurements for parametric and nonparametric data, respectively.

RESULTS

The study included 79 individuals with PTH values below the reference range (reference range: 15-65 pg/mL). Five (6.32%) of the individuals were male, and 74 (93.67%) were female. The minimum age was 29 years, the maximum age was 75 years, and the mean age was 49.62±11.60 years. PTH, calcium, phosphorus, ALP, and vitamin D levels and their statistical relationships were calculated (Table and Figure).

When PTH measurements were compared with calcium and phosphorus products, it was observed that PTH level had no statistically significant effect on the product of calcium and phosphorus levels (p=0.70), mean phosphorus level (p=0.37) and mean calcium value (p=0.21).

Table . The relationship between PTH, Ca, P, ALP, and vitamin D values of individuals

	Minimum	Maximum	Mean	Reference values	Comparison with PTH
Ca value	6.10 mg/dl	10.27 mg/dl	8.57 ± 0.90	8.8-10.6 mg/dl	p = 0.70
P value	1.80 mg/dl	7.80 mg/dl	4.46 ± 0.99	2.5-4.5 mg/dl	p = 0.37
Ca X P	19.80	61.75	37.64 ± 7.37	Ca X P < 55	p =0.21

PTH: parathormone, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, p<0.05 not significant

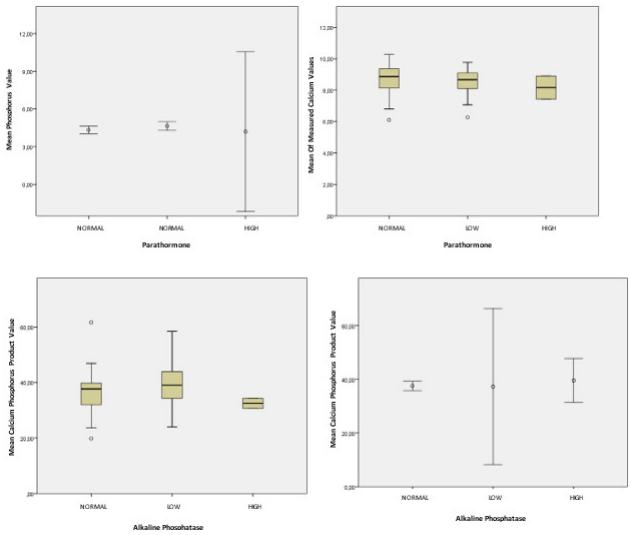

Figure. Parathormone, phosphore, calcium; alkalin phosphatase, calcium phosphatase graphics

Calcium and phosphorus levels can be regulated externally, even if the patient has hypoparathyroidism. Although the loss of parathyroid tissue in these patients requires continuous external medical treatment, it was also shown that it can be kept as regular as a healthy individual with medical treatment.

There was no statistically significant correlation between measured ALP levels and calcium phosphorus products (p; 0.866). Similarly, no statistically significant correlation was found between PTH levels and ALP measurements (p; 0.131). This indicates that the reason for this situation is due to the calcium and phosphorus values that were tried to be normalized with the treatment.

In the comparison between PTH levels and vitamin D levels, no statistically significant difference was observed when the values were grouped as low, medium, and high (p value; 0.681).

In other analyses, no statistical correlation was found between creatinine value and mean calcium value, mean phosphorus value, and calcium phosphorus product value (p values=0.692, 0.281, and 0.439, respectively). Because the creatinine values of all patients were within the reference range.

The result shows that kidneys in the reference range can support regulation and do not disrupt calcium-phosphorus balance.

All the patients were receiving hormone replacement therapy because of the thyroidectomy. However, the euthyroid state of the patients periodically deteriorated during follow-up. When the results of that period were examined, no statistically significant difference was found between the mean calcium and phosphorus levels and the calcium-phosphorus product values of hypothyroid and non-hypothyroid patients (p values 0.606, 0.599, and 0.404, respectively). Again, the result shows that calcium-phosphorus metabolism is completely in the hands of the individual in these patients, and we can preserve bone mineralization as much as possible with treatment compliance.

DISCUSSION

Hypoparathyroidism, one of the complications of thyroid surgery, is observed at a lower rate in experienced surgeons. It is very important to minimize this complication, which is preventable in some patients, considering that patients will receive lifelong medical treatment.[7] Hypoparathyroidism secondary to thyroid surgery was found to be a high etiologic factor in our patients, in accordance with the literature. In the study by Karakoç et al.[8] transient hypocalcemia was found in 63% of thyroidectomized patients. It was reported that the remaining 37% of patients needed lifelong medical treatment. In our study, transient hypoparathyroidism was ruled out because there were patients who had been receiving hypoparathyroidism treatment for at least one year.

There are many mechanisms that regulate calcium-phosphorus balance and, thus, the musculoskeletal system. The parathyroid gland is one of them and is very important. Loss of the parathyroid gland causes disruption of calcium and phosphorus metabolism.[9] Another major system that provides this balance is renal regulation.[10] Our data shows that there is no statistically significant relationship between the glomerular filtration rate and calcium phosphorus values. Because the creatinine values and glomerular filtration rates of all our patients were within the normal range. Thus, we were able to evaluate the effect of parathyroid tissue more clearly by ignoring renal regulation. Another system is the gastrointestinal system; its proper and effective functioning is especially important for the effectiveness of the treatment. Kartal et al.[11] showed how malabsorption and previous gastrointestinal surgeries can cause osteoporosis.

In a study by Demir et al.[12] it was observed that the use of teriparatide in the treatment of osteoporosis reduced the risk of fracture formation, and the importance of parathormone in osteoporosis and osteoporosis-related fractures was emphasized. Since we aimed to see the effect of the parathyroid gland only by eliminating other factors as much as possible in our study, patients with renal failure were not included in our study, and patients with known diseases affecting the gastrointestinal system, surgery, and patients taking medication were not included. However, it was observed that the calcium doses required by patients with the same PTH levels were different, even though standardization was attempted. Because many factors, including body mass index, age, and absorption levels, affect calcium and phosphorus levels. For this reason, patients should be given calcium and vitamin D replacement based on the target ranges of the Turkish Society of Endocrinology and Metabolism (TEMD); it was observed that not everyone's needs are the same due to the different doses of drugs used by our patients. Pregnancy is also an example; the increased PTH-relasing peptide cannot function in the absence of parathyroid tissue; higher doses of treatment are required to meet the increased need for pregnancy.[13]

Options for the treatment of hypoparathyroidism are being developed because the need for lifelong medical treatment is exhausting for patients in every sense. Issues such as parathyroid tissue auto transplantation or donor transplantation with immunosuppression support are widely discussed in the scientific community.[14] Kanımdan et al.[15] obtained very successful results in this regard in their studies on rats. Idiz et al.[16] suggested that severe hypocalcemia attacks could be prevented with auto transplantation; however, it was reported that this was not possible in every center, and cryopreservation laboratories were needed. In another study, it was concluded that functional parathyroid gland conjugates could be produced by 3D printing. Many such methods have been tried.[17] However, today, instead of these treatments, which have very limited applicability, deficient mineral-assisted therapy is applied. All our hypoparathyroid patients receive medical treatment. They use calcium and vitamin D as medical treatments. Since the patients were under medical treatment, the mean values of calcium 8.57±0.90 (n: 8.8-10.6) and phosphorus 4.46±0.99 (n: 2.5-4.5) were found to be normal or close to the normal range. Yüksel et al.[18] examined the factors affecting hypocalcemia after thyroidectomy and concluded that vitamin D should be corrected preoperatively.[18] An example of this is a case in which a patient with pseudohypoparathyroidism improved with vitamin D replacement.[19] In our study, in order to eliminate the vitamin D factor, calcium and phosphorus values measured when vitamin D was in the reference range were included in all our patients.

In our study, no significant correlation was found between the PTH value and both calcium, phosphorus, and calcium phosphorus products ($p<0.05$). The reason for this was thought to be the fact that all patients were under treatment, and these improvements were achieved with external calcium and vitamin D treatment. However, in the case of hypoparathyroidism, low calcium and high phosphorus levels are expected to result in disturbances in calcium-phosphorus balance.[20] In our study, it was observed that the effect of hypoparathyroidism on bone mineral disorders could be prevented by correcting calcium-phosphorus metabolism with external medical treatment; however, it is still not possible to completely replace the lost tissue.

Limitations of the study: Retrospective nature and lack of confirmation by bone densitometry or bone biopsy as bone mineralization indicators.

CONCLUSION

We may face loss of parathyroid tissue as a complication of thyroidectomy. Our study shows that the preservation of parathyroid tissue is, of course, important. However, it is equally important that calcium-phosphorus metabolism be kept in balance with appropriate treatment in these patients. Thus, complications due to hypoparathyroidism can be minimized. Although it is not possible to completely cure the deficiency of the parathyroid gland in adequately

treated hypoparathyroid patients, bone mineralization can be preserved to a great extent.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committee of Yozgat Bozok University (Date: 10.11.2022, Decision Number: 2017-KAEK-189_2022.11.10_07).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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